REMARKS

Consideration of references submitted in Information Disclosure Statements

The Examiner indicates that the references Zav'Yalov et al. Mol. Immunol., 32:425-431 (1995) and Zarogoulidis et al. Lung-Cancer, 15:197-205 (1996) were not considered because he could not locate copies of the references. The references were crossed-out on the PTO-1449 submitted on November 29, 1999. However, the Examiner then acknowledges consideration of the references on the PTO-1449 submitted on February 28, 2000. (These references were resubmitted with the February 28, 2000 IDS after receipt of the Notification of Missing Requirements issued January 12, 2000, which indicated copies of the references cited in the International Search Report had not been received from the IB.) Clarification of whether the above-two references have been considered is respectfully requested.

The Examiner further indicates that reference FR 2706772 was not considered. Applicants respectfully note that FR 2706772 was cited on the English language International Search Report, a copy of which was submitted with both the November 29, 1999 and February 28, 2000 IDS's and which was also forwarded by the IB to the USPTO.

As such, the Examiner must consider this reference. See M.P.E.P. §609(A)(3).

Abstract of the Disclosure

The Examiner indicates that the Abstract of the Disclosure is not in proper form for U.S. applications. The specification has been amended as indicated above to insert the attached Abstract of the Disclosure. The Abstract in no way adds new matter.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1 and 3-5 have been rejected under 35 U.S.C. §112, second paragraph as being unclear. More specifically, claim 1 has been rejected as being unclear in the recitation of "such as" and "corresponding to." Claim 1 has been amended for clarity to delete the recitation of these terms.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1 and 3-11 have been rejected under 35 U.S.C. §112, first paragraph for lack of written description. The Examiner asserts that Applicants were only in possession of compositions comprising immunosuppressants and bioactive peptides consisting of

SEQ ID NO:1 and SEQ ID NO:2. The Examiner asserts that one skilled in the art cannot envision all the possible amino acid sequences encompassed in the present claims. The Examiner also asserts that Applicants have not disclosed any bioactive peptides corresponding to a high affinity binding site/antilymphoproliferative activity other than SEQ ID NOS:1 and 2. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The Examiner asserts that Applicants only disclose the bioactive peptides corresponding to a high affinity binding site/antilymphoproliferative activity of SEQ ID NOS: 1 and 2 and that Applicants were not in possession of a sufficient number of peptides at the time of the invention so as to represent a genus that supports the claimed invention.

However, the Examiner is incorrect in her evaluation of the invention. SEQ ID NOS: 1 and 2 include numerous peptides falling within the scope of the invention so as to represent a genus. Page 8, lines 22-29 of the specification discloses that it is straight forward and does not require undue experimentation to locate an active site within an interferon (i.e. the high affinity binding/antilymphoproliferative site) and to produce a bioactive peptide corresponding to the site. From this disclosure it is evident that the inventors contemplated bioactive peptides other

than SEQ ID NOS:1 and 2 as part of the invention and how to obtain such peptides. In addition, the chimeric protein, albeferon, which is disclosed and tested in the specification, is an example of a recombinant protein of the invention. As such, the specification fully describes the invention as claimed and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102

Claim 6 has been rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Pat. No. 5,747,034. The Examiner asserts that the '034 patent discloses a composition containing a therapeutically effective amount of an antibody or antigen-binding fragement (bioactive peptide) and an immunosuppressant agent selected from cyclosporin A, FK506, rapamycin and corticosteriods.

Claim 6 has been cancelled, thus obviating this rejection.

Rejections under 35 U.S.C. §103

Claim 1 has been rejected under 35 U.S.C.§103 as being obvious over Charak et al. combined with Cruse et al. Charak et al. is relied on for teaching compositions comprising cyclosporin A and interferon and that the use thereof after chemotherapy to generate an anti-tumor effect and the adoptive transfer of MHC-bearing cells

to secondary tumor bearers treated with chemotherapy had an antitumor effect. The Examiner asserts that Charak et al. differs from the invention of claim 1 in failing to teach a recombinant protein having the sequence of IFN α, β, τ, or ω. Cruse et al. is relied on for teaching interferons that have immunomodulatory functions and that IFN α has anti-proliferative properties. The Examiner asserts that it would have been obvious to substitute the specific interferons of Cruse et al. for the generic interferon of Charak et al.

Claims 1, 3 and 5-11 have been rejected under 35 U.S.C. §103 as being obvious over Charak et al. combined with Zav'Yalov et al. Further to the teachings of Charak et al. Zav'Yalov et al. is asserted to teach SEQ ID NOS: 1 and 2. The Examiner asserts that it would have been obvious to use the proteins of Zav'Yalov et al. in the compositions of Charak et al.

Claim 4 has been rejected under 35 U.S.C. §103 as being obvious over Charak et al. and Zav'Yalov et al. combined with Isoai et al. Further to the teachings of Charak et al. and Zav'Yalov et al., Isoai et al. is asserted to teach binding peptides to a macromolecule for stabilization. Isoai et al. is asserted to teach the linking of peptides to albumin for stabilization and to increase the serum half-life of the peptide.

Claims 2, 3, 5-6 and 8-10 have been rejected under 35 U.S.C. §103 as being obvious over Charak et al. combined with WO 94/01457 or Ruegg et al. WO '457 is asserted to teach SEQ ID NO:1 as an interferon binding peptide for pharmaceutical compositions. Ruegg et al. is asserted to teach a decapeptide of IFN-α which inhibits proliferation of lymphoblastoid cell lines.

Claim 4 has been rejected under 35 U.S.C. §103 as being obvious over Charak et al. combined with WO 94/01457 or Ruegg et al. and Isoai et al. Isoai et al. is again relied on for teaching the coupling of a peptide to a macromolecule, such as albumin, for stabilization and increased serum half-life.

Claims 1 and 6 are rejected under 35 U.S.C. §103 as being obvious over Charak et al. combined with WO 94/10313. WO '313 is relied on for teaching IFN-τ peptides having antiproliferative properties and which do not have cytotoxic side-effects.

Claim 4 has been rejected under 35 U.S.C. §103 as being obvious over Charak et al. combined with WO '313 and Isoai et al. Isoai et al. is again relied on for teaching the coupling of a peptide to a macromolecule, such as albumin, for stabilization and increased serum half-life.

Applicants traverse these rejections and withdrawal thereof is respectfully requested. Each of the rejections under 35 U.S.C.

§103 relies on Charak et al. as a primary reference. The Examiner's evaluation of this reference and the teachings thereof in relation to the present invention are incorrect. As such, the following remarks pertaining to Charak et al. are applicable to all of the rejections.

The Examiner premises the rejections on the disclosure in Charak et al. of a method of reducing the side-effects of cancer treatments. However, the present invention is not drawn to a method of reducing the side-effects of cancer treatments. The present invention, as encompassed by amended claim 1, is drawn to a method of amplifying activity of immunsuppressants to reduce the needed therapeutic dose and associated side effects during the treatment of diseases wherein cyclosporins, FK506 or rapamycin can be exploited (i.e. which are responsive to cyclosporins, FK506 or rapamycin).

As noted above, The Examiner relies on the disclosure in Charak et al. of anticancer drugs and cancer treatment as a primary reference. However, Charak et al. fails to teach the method of the present invention as suggested by the Examiner. The present invention of amended claim 1 defines the disease as one that is responsive to cyclosporins, FK506 or rapamycin. However, it is well-known in the art that cyclosporins, FK506 and rapamycin cannot

be used to treat cancers. As stated on page 1, lines 22-24, of the specification "cyclosporins' systemic use have been associated with..., increased incidence of lymphoid tumors." In addition, page 4, lines 10-12, state that "systemic administration of cyclosporins...creates risks for other diseases including cancers." As such, Charak et al. is inapplicable to the present invention and does not disclose the method of the present invention.

The method of the present invention does not enhance the activity of IFN-α-derived peptides by combining them with immunosuppressants. Rather, the present invention enhances the activity of the immunosuppressants by combining them with the recited bioactive peptides. None of the references relied on by the Examiner disclose the enhancement of the activity of immunosuppressants. As such, the invention is not achieved by the references.

The Examiner is correct that Charak et al. disclose the combination of immunosuppressants and interferons to obtain an anti-tumor effect. However, that teaching is irrelevant to the present invention. There is no teaching in Charak et al. regarding the enhancement of the activity of immunosuppressants and as discussed above, cyclosporins, FK506 and rapamycin cannot be used to treat cancers. As such, one skilled in the art would have no motivation

to combine the Charak et al. with Zav'yalov et al. or the other relied on secondary references. Withdrawal of the rejections is therefore respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D. (Reg. No. 40,069) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

A marked-up version of the amended parts of the specification and claims showing all changes is attached hereto.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $200.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Marked-up Version Showing Changes

IN THE ABSTRACT

The attached Abstract of the Disclosure has been inserted into the specification.

IN THE CLAIMS

Claims 6-11 have been cancelled.

Claims 1, 4 and 5 have been amended as follows.

1. (Thrice Amended) A composition comprising immunosuppressants, cyclosporins, FK506, or rapamycin and at least one bioactive peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of interferons α, β, ω, τ, or recombinant proteins carrying one or more of the sequences corresponding to the structures of ~~the~~ **said** bioactive peptides ~~corresponding to the high-affinity binding/anti-lymphoproliferative site of the said interferons~~ for the aim of amplification of immunosuppressants' activities to decrease their therapeutic dose, and as the consequence to avoid their undesirable side effects during organ and tissue transplantation or during treatment of **diseases** ~~cancers such as lymphomas, leukemias, myelomas, adenocarcinomas, autoimmune and chronic inflammatory diseases, such as rheumatoid arthritis, myasthenia gravis, lupus erythematosis,~~

~~uveitis, hyperproliferative diseases, such as psoriasis vulgaris,~~ wherein cyclosporins, FK506 or rapamycin can be exploited.

4. (Twice Amended) The composition according to Claim 5 wherein the ~~at least one~~ **bioactive** peptide is genetically or chemically modified or genetically or chemically or physically bound to a small-molecular or macromolecular substance increase the stability of the ~~at least one~~ **bioactive** peptide in physiological conditions or for regulating the bioavailability of the ~~at least one~~ **bioactive** peptide.

5. (Amended) The composition according to claim 1, comprising at least one cyclosporin, rapamycin or FK506 and ~~at least one~~ **a bioactive** peptide ~~having~~ **consisting of** the amino acid sequence of SEQ ID NO. 1 or being a variant of SEQ. ID NO. 1 that is SEQ. ID. NO. 2 such that zero to three amino acids of SEQ ID NO. 1 are substituted.

New claim 19 has been added.